PARTNERS HUMAN RESEARCH COMMITTEE DETAILED PROTOCOL

Treating Depression in Patients with De Quervain's tenosynovitis; An integrated web based skills intervention and decision aid

DETAILED PROTOCOL

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I. BACKGROUND AND SIGNIFICANCE

De Quervain's tenosynovitis is prevalent and treated with discretionary medical approaches. De Quervain's tenosynovitis is a self limiting condition involving tendinosis of the abductor pollicis longus (APL) and extensor pollicis brevis (EPB) tendons within the first extensor compartment of the wrist[1]. It has a prevalence of 1.3-2.1% in women and 0.5-0.6% in men[2]. The standard care treatment for de Quervain's tenosynovitis includes a variety of medical options including nonsteroidal anti-inflammatory medication (NSAIDs), orthoses, corticosteroid injections and surgery[3], One study showed a significant variation in use of corticosteroid injection and surgery between 10 hand surgeons in 2 medical centers[4]. Because de Quervain's tenosynovitis is a self-limiting condition surgery is discretionary[4].

Depression and coping explain the challenges faced by many patients in managing de Quervain's. Research has shown that there is limited correlation between impairment and disability is in many orthopedic conditions[5]. A biopsychosocial model that considers the complex interactions of biological, psychological and social variables may explain this discrepancy[6]. Indeed, studies have shown that depression affects patient reported outcome measures in de Quervain's tenosynovitis[7]. Disability is significantly correlated with symptoms of depression, anxiety, pain-escaping behavior[8], and catastrophizing[7 9]. Multivariable linear regression models showed symptoms of depression accounted for 32% of the variability in functional outcomes[7], suggesting that depression is a risk factor for poor outcomes in patients with de Quervain's tenosynovitis.

Psychosocial skills interventions that target depression may improve outcomes in patients with de Quervain's. A number of studies have shown that psychosocial treatments that are focused on teaching coping skills are effective in improving depression[10] as well as decreasing disability across many conditions from fibromyalgia[11], tinnitus distress[12] to chronic pain[13]. Depression also predicts outcomes after elective minor surgeries include de Quervain's[14]. The multidisciplinary team at MGH has developed a 4 session psychosocial skills intervention (Toolkit for Optimal Recovery)[15] for patients with acute musculoskeletal trauma at risk for persistent pain and disability, which has been shown to improve pain at rest function, pain with activity, pain catastrophizing, depression and pain anxiety when compared to standard care[5 15]. This intervention may also be beneficial for individuals with de Quervain's who also report depression. To date, there are no studies of psychosocial interventions to improve outcome in individuals with de Quervain's tenosynovitis. Treating depression represents an unexplored

opportunity to improve outcomes for patients with de Quervain's tenosynovitis regardless of the medical treatment modality they choose.

Decision aids may help patients make a more informed choice about their treatment for de Quervain's and depression. Decision aids (DA; shared decision making tools—websites, videos, or pamphlets) are interventions to prepare patients to make more informed and satisfying decisions that match their preferences and values. DA's are designed to provide patients with balanced, complete and understandable information about their options as well as risks and benefits, in order to help them determine their preferences according to their values[16]. A systematic review of decision aids for treatment or screening decisions found participants felt more knowledgeable and better informed with a more active role in decision making[17]. A decision aid component that educates patients about their depressive symptoms and association with symptoms and disability may also be a more sensitive and cost effective way to get timely treatment for patients in need. By being more involved in the treatment choice, patients can feel empowered and may show better recovery.

This study aims to develop a decision aid (DA) for helping patients with de Quervain's tenosynovitis to determine their preferences for treatment (including treatment for depression for those with clinical depression) according to their values and relationship with pain and disability.

II. SPECIFIC AIMS (Research Objectives)

Aim 1: To develop a feasible and acceptable decision aid (DA) combined with a web-based depression treatment (Toolkit-depression) to help patients with de Quervain's tenosynovitis make informed choices with regard to their treatment, for de Quervain's tenosynovitis and comorbid depression.
Hypothesis: NA

Aim 2: To conduct an RCT of patients with de Quervain's tenosynovitis and compare patients who screen in for depression and are randomized to the Toolkit-depression versus patients who screen in for depression and undergo enhanced usual care (EUC). Primary outcomes are: pain intensity (NRS pain) and disability (DASH). Secondary outcomes are depression and catastrophic thinking about pain.

Hypothesis 1a: The DA will be feasible (>75% of participants will agree to participate) and accepted by patients (scores on the Client Satisfaction Scale above median split).

Hypothesis 1b: The Toolkit-depression will be feasible (>75% participants randomized to the Toolkit-depression will agree to participate and complete at least 3 out of the 4 web modules) and accepted by patients (scores on the Client Satisfaction Scale above median split).

Hypothesis 2: Patients randomized to Toolkit-depression will show short-term (pre to post) improvements in both primary and secondary outcomes when compared to those

randomized to enhanced usual care. Improvements will be both statistically and clinically significant.

Hypothesis 3: Patients randomized to Toolkit-depression will show similar improvement (pre to post) in both primary and secondary outcomes when compared to those who did not screen in for depression and did not use the Toolkit.

Aim 3: To determine if improvements are durable at 6 month follow up.

Hypothesis 3: Among patients who screen in for depression, those randomized to Toolkit-depression will show sustained (post 6 months) improvements in both primary and secondary outcomes when compared to those randomized to EUC. Improvements will be both statistically and clinically significant.

III. SUBJECT SELECTION

We will use three recruitment methods in this study:
1. First contact via invitation letters to patients with specific mention of de Quervain's or symptoms thereof per referral or clinical notes;
2. First contact during clinical visit for patients with possible de Quervain's per symptoms documented in referral or clinical notes;
3. First contact made by patients to study staff in response to study advertisement on clinicaltrials.partners.org

Inclusion criteria
Adults (≥18 years) diagnosed with de Quervain's tenosynovitis
English fluency and literacy
Ability to give informed consent

Exclusion criteria
Inability or unwillingness to participate in decision aid (DA) and/or Toolkit-depression
Major medical comorbidity expected to worsen in the next 6 months
Comorbid chronic pain condition
Antidepressant medications changes in the past 6 months
Severe and untreated mental health conditions or active substance dependence
Secondary gains such as litigations or worker compensation procedures that may interfere with patients' motivation for treatment
No online device available to use the DA and Toolkit-depression

IV. SUBJECT ENROLLMENT

Recruitment by screening clinic schedule
Potential subjects will be identified by screening the schedule of the Hand and Arm Center at Massachusetts General Hospital. For patients referred to a hand surgeon with a probable diagnosis of de Quervain's tenosynovitis, a recruitment letter may be sent to them by mail or via

Patient Gateway. The letter explains the purpose of the research - study procedures, and duration of participation.

Patients who opt in to the study and will be contacted by study staff to explain the study, obtain consent from the subject and answer all remaining questions. Subjects that agree to participate will electronically sign the consent form in REDCap. Subjects will receive a copy of the consent form via e-mail.

Patients will therefore have the opportunity to start working with the decision-aid prior to their appointment and be able to make a more informed decision making process with the specialist. They will also be asked to complete enrollment questionnaires, including PHQ-9 for symptoms of depression.

Recruitment at clinic attendance
Patients whose referrals do not mention de Quervain's specifically but that could be presenting for de Quervain's or patients whose appointments are made close enough in the future that it is not logistically feasible to contact them for pre-screening will be approached in clinic by study staff. Study staff will briefly describe the study and ask if the patient may be interested in participating if eligible. If the patient agrees, they will be asked to sign the consent form and proceed with the pre-screening questionnaire (PHQ-9) and DA. They will also be asked to complete enrollment questionnaires before their consultation.

Advertisements on clinicaltrials.partners.org
We will create a study card on Partners' clinicaltrials.partners.org website to advertise our study. Patients who are interested can contact the study staff to learn more about the study. Subjects that agree to participate will electronically sign the consent form in REDCap. Subjects will receive a copy of the consent form via e-mail. They can then start working with the DA and complete the enrollment questionnaires including the PHQ-9. Patients can schedule an appointment with one of the participating hand surgeons.

For all patients, during their consultation a hand surgeon will confirm the diagnosis of de Quervain's. Patients that do not have de Quervain's tenosynovitis will be excluded from the study.

After the initial appointment with the specialist, patients with a diagnosis of de Quervain's tenosynovitis and symptoms of major depression will be randomized to the Toolkit-depression (Cohort 1) or Standard Care (Cohort 2). The randomization is done within REDCap via generated randomization sequence. Subjects randomized to the Toolkit-depression will be given the online link to the Toolkit.

V. STUDY PROCEDURES

This study will employ a randomized, prospective design. The patients will be randomly assigned to two different cohorts after the encounter with the physician. The physician will be informed that the patient is participating in this study, but will not know to which cohort the patient will be

randomized.

At enrollment, demographic data will be collected, including age, gender, ethnicity, race, marital status, current work status, consulting hand surgeon, occupation, education, hand dominance, affected side and current analgesia intake. They will also be asked to complete surveys to assess pain intensity (NRS), disability (QuickDASH), depression (PHQ-9) and catastrophic thinking (PCS-13) on REDCap. Participants randomized to Toolkit-depression will be given a link to access the Toolkit online at home.

Cohort I will be managed with the Toolkit-depression and cohort II will be managed with standard care. The patients in Cohort I will receive a link to the Toolkit that they can complete in at home. The Toolkit consists of 4 sessions focused on teaching relaxation strategies as well as cognitive and behavioral aspects of acute pain.

Outcome: Measured variables at enrollment – with REDCap, which will take approximately 20 minutes to complete:

Demographic data (at enrollment)
Patients: age, gender, ethnicity, race, marital status, current work status, consulting hand surgeon, occupation, education, income, hand dominance, affected side, current analgesia intake

Depression symptoms (at enrollment, 6 weeks and 6 months)
The Patient Health Questionnaire 9 (PHQ-9) involves questions about how often a patient has been bothered by 9 symptoms of depression in the last 2 weeks. It can be used to establish a diagnosis of depression as well as grade depressive symptom severity[18]. Compared to structured interview with a mental health professional, the PHQ-9 score of $\geq$10 has a sensitivity and specificity of 88% for major depression[18].

Outcome measures (at enrolment, 2 weeks, 6 weeks and 6 months)
Outcomes will be measured at enrollment and 6 weeks after initial assessment, as this corresponds to the end of the Toolkit-depression. They will also be measured at 6 months follow up. At 2 weeks they will be asked about the type of treatment received and their satisfaction with the DA (CSQ-3) as well as any decisional conflict (DCS).

In a single-center study of patient-centered care for de Quervain's tenosynovitis, 57% of patients who opted for non-operative treatment noted resolution of symptoms within 6 months[3]. In an RCT of full-time compared to as-desired splint wearing for patients with de Quervain's tenosynovitis, DASH score only improved by a mean of 7 points at follow up after 8 weeks[7]. The minimum clinically important difference in DASH score is approximately 10[7 19] so it would be better to wait until 6 months when symptoms are more likely to have resolved.

Primary outcome measure:
Disability: QuickDASH score (Disabilities of the Arm, Shoulder and Hand score)
The QuickDASH score questionnaire asks about pain and function related to activities using a patient's upper limbs. It involves 11 questions, and is scored 0-100 where 0 represents the least pain and best function.

Secondary outcome measures:
Depression (PHQ-9)
Catastrophic thinking about pain (Pain Catastrophizing Scale)
Decisional Conflict Scale (DCS)

About the Toolkit-depression
Treatment satisfaction (Client Satisfaction Questionnaire CSQ-3)

About the Decision Aid
Satisfaction (Client Satisfaction Questionnaire CSQ-3)

VI. BIOSTATISTICAL ANALYSIS

Statistical issues
A minimum sample size of 54 patients would allow the study 90% power to detect a difference of 15 points in QuickDASH score between patients who received the Toolkit-depression intervention and those that did not[7]. Therefore we would want to enroll a minimum of 27 patients in each group. There will be 3 groups compared: those without symptoms of major depression who have used the DA, and those with symptoms of major depression who have been randomized to the Toolkit or Enhanced Standard care.

A study of de Quervain's tenosynovitis in 2 academic centers in Boston, recruited 2513 patients over 12 years[4] equating to approximately 200 patients per year.

In an RCT of the Toolkit, 14% did not complete the intervention[5]. If we anticipate experiencing similar levels, we will need to recruit a minimum sample size of 90 patients.

In a study of depression in patients with common hand diagnoses, 46% of patients with de Quervain's tenosynovitis had a PHQ-9 or CES-D score consistent with symptoms of major depression[20]. However, this may be as low as 10%[21]. Therefore it may take between 6 months and just over 2 years to recruit 70 participants to our trial.

Chi-square tests will be conducted to determine the differences between two categorical variables. Independent Student's t-tests will be performed to determine the differences between continuous and dichotomous variables. Paired samples T-test will be used to compare the mean scores for the same group on different occasions. ANOVA will be used to analyze the difference between the 3 groups.

Pearson's correlation or Spearman correlation will be used to explore the strength of the relationship between the conflict of decision-making and the use of decision aids. Wherever the minimum expected cell frequency is less than five, the Fisher's exact test will be used instead of the Pearson's Chi-square test.

All variables with significant ($p<0.05$) or near significant ($p<0.08$) relationships will be evaluated with backwards multivariate/binary logistic regression (depending on the outcome variable)

Descriptive statistics will be summarized in terms of means, standard deviations or frequencies, and will be calculated at each time point. Incomplete data will be adequately described and mean imputation will be used when deemed necessary. We will use IBM SPSS ® (24) to perform the data analysis.

VII. RISKS AND DISCOMFORTS (Stratify by common and uncommon)

Since all patients will receive the usual care, participation in this trial does not impose additional risks to the patients. This trial does not interfere with the surgical process or postoperative care. If the completion of questionnaires causes discomfort for patients, Study physicians will be readily accessible for consultation.

There is the possibility that some patients are initially identified as having de Quervain's tenosynovitis and complete enrollment questionnaires, but having seen the Specialist Hand Surgeon it is determined that they do not have de Quervain's tenosynovitis. This may be distressing for some patients. However, this did not pose any problems in a recent study at this center (IRB Protocol Number 2015P002550) when 12 patients were excluded after initial likely diagnosis of thumb carpometacarpal joint arthritis but were later excluded due to a different diagnosis.

Where a participant PHQ-9 score indicates symptoms of severe depression (PHQ-9 $\geq$20), REDCap will notify Dr Vranceanu, a clinical psychologist, who will be able to conduct a psychological assessment of the patient's safety (including suicidality).

The greatest discomfort associated with participation is the time required to complete the Toolkit-depression that is estimated to take 30 minutes to complete each of the 4 sessions. Additionally, the questionnaires at enrolment, 6 weeks and 6 months will take approximately 20 minutes to complete, but this can be done online via REDCap at home.

VIII. POTENTIAL BENEFITS

For subjects receiving standard care, there will be no direct benefit since the treatment represents standard care. We hope that patients managed with the Toolkit-depression may experience improvement in their symptoms of depression as well as improvement in pain intensity and disability in terms of their de Quervain's tenosynovitis. The study may also benefit society as a whole by providing a better understanding of the factors that influence patient-reported outcomes in de Quervain's tenosynovitis.

Subjects will not receive monetary remuneration for their participation in this study. Since the patients have to return to the Hand and Arm Center for their regularly scheduled follow-up and the questionnaires are being sent online via REDCap, there are no additional monetary costs associated with participation in this study.

IX. MONITORING AND QUALITY ASSURANCE

There will be a full-time research coordinator and principal investigator responsible for adherence to all IRB rules and guidelines and for the accuracy and completeness of all forms, entries, and informed consent.

Study physicians will be readily accessible for consultation should a study patient experience increasing discomfort while completing the questionnaire.

Adverse events
Adverse events are defined as harmful occurrences to study participants, either study related or non-study related. The principal investigator will be responsible for insuring that any adverse events are reported to the IRB or federal agencies as necessary. Adverse events will be reported to the IRB in compliance with Partners policy as they are discovered by any study staff member and discussed with the PI or designee. The research coordinator, supervised by the principal investigator will be responsible for cataloging and tallying adverse events. Serious adverse events (SAEs) will be reported to the PHRC in accordance with Partners policy. All proposed staff have participated in the NIH required trainings in participation and conduct of studies that involve human subjects, and any future study staff will do so upon hiring. If any study staff discovers any untreated condition (e.g. onset of substance abuse or physical condition), they will refer participants to appropriate treatment immediately. Study staff will follow Massachusetts's laws regarding mandated reporting for psychologists (i.e. discovery of abuse to a child, elder, or disabled person, participant is imminent danger of hurting themselves or an identifiable other person). Fluctuations in depressed mood (that do not involve suicidality) are not considered adverse events.

Study data
Study data will be maintained in a locked filing cabinet and on password protected computers. Questionnaires and self-reported responses will not become part of the subject's medical record. Hardcopies of study related data and forms will be stored in a lockable file cabinet or converted to certified digital copies and originals shredded. Subject information will remain confidential by keeping identifying information (name and subject number) in a separate locked file cabinet or password protected computer or approved database (REDCap). Only the investigators and study staff specified on the protocol will have access to this information. Any magnetic or electronic information will be saved in password-protected computers to which only research coordinator and persons involved with the research project will have access. REDCap, secure and HIPAA-compliant, will be used to collect all answers. The Principal Investigator oversees and monitors this process.

Study data will be collected and managed electronically using REDCap, a free online research management tool. It enables researchers to create study-specific websites for capturing participant data securely. Measures within the REDCap library can be included as well as custom instruments created or entered by the researcher. Patients can log in to complete online questionnaires.

REDCap enables customization of item or instruments (e.g., format, randomization, skip patterns), storage of protected health information in a separate, secure database, automated accrual reports, real-time data export, among many other features. REDCap is well secured and

effectively protected and a compliant application that includes databases which store confidential, personal health information.

Any magnetic or electronic information will be saved in Partners password-protected computers to which only research coordinator and persons involved with the research project will have access.

Care will be taken to preserve the confidentiality of patient information. Research data will not become part of the medical record. Patient information specific to the study will be maintained in a private database on a secure network, to which access is limited. Hardcopies of study related data and forms will be stored in a lockable file cabinet or converted to certified digital copies and originals shredded. All participants are given a participation number/code at the time of enrollment. Subject information is only accessible by Partners authorized investigators and outside investigators who have been approved by the data use agreement process by the IRB and Research Management. Subject information will not be accessible to any of the referring hand surgeons at non-Partners sites.

All data will be maintained at MGH in accordance with Partners policy. Data may be shared and stored as a limited data set with non-Partners investigators through a Data Use Agreement (DUA) with approval of the IRB and Research management. Non-Partners investigators may temporarily store the data on password protected, encrypted laptops.

Once the research is complete, all direct patient identifiers will be destroyed.

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